Global patterns of use of antithrombotic and antiplatelet therapies in patients with acute coronary syndromes: Insights from the Global Registry of Acute Coronary Events (GRACE)

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Background Many agents are available to treat acute coronary syndromes (ACS), yet limited information is available about their use from a multinational perspective. The objective of this report was to describe patterns of use of antithrombotic and antiplatelet therapies in patients with the spectrum of ACS through the use of data from the Global Registry of Acute Coronary Events (GRACE).

Methods Data from 12,665 patients with ACS were analyzed. Baseline characteristics, clinical presentation, and medication use were compared. Regional differences in the administration of antiplatelet and antithrombotic therapies were analyzed. Multivariable logistic regression was implemented to determine independent variables indicating the use of various hospital therapies.

Results Overall, unfractionated heparin was used in 57% of patients and low-molecular-weight heparin in 47% ($P < .0001$). More than 90% of patients received aspirin, but approximately 13% were not discharged on aspirin. Overall, 30% of patients received thienopyridines (with percutaneous coronary intervention [PCI] in 79%). Of those who did not receive aspirin, 31% received thienopyridines. Intravenous glycoprotein inhibitors were given to 17% of patients. Among those treated with PCI, only 47% received glycoprotein inhibitors, and 21% of those given glycoprotein inhibitors did not undergo PCI. Significant geographic variation was apparent in the use of unfractionated heparin, low-molecular-weight heparin, thienopyridines, and glycoprotein inhibitors.

Conclusions Despite the availability of guidelines, striking geographic and practice variations are apparent in the use of antithrombotic and antiplatelet therapies. There remains significant room for improvement in the use of these therapies in patients with ACS, which should lead to improvement in care and outcomes. (Am Heart J 2003;146:999–1006.)

Practice guidelines have been developed for the use of antithrombotic and antiplatelet therapies in acute coronary syndromes (ACS).[1–4] Traditionally, the standard therapies were aspirin and unfractionated heparin (UFH).[5,6] Recently, clinical trials of low-molecular-weight heparin (LMWH), direct thrombin inhibitors, thienopyridines, and glycoprotein (GP) IIb/IIIa inhibitors have identified additional or alternative effective therapies for patients with ACS.[7–10]

Clinical guidelines[1–4] are based on data from clinical trials performed in highly selected patient populations. Relatively little information is available regarding the use of recommended therapies in routine clinical practice. Furthermore, the heterogeneous presentation of ACS leads to variation in its diagnosis and treatment,[2,4] and geographic variations exist in the treatment of patients with ACS.[11] The aims of this report are to describe current hospital use of antithrombotic and anti-

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platelet medications and to identify factors that may predict the use of these therapies using data from the Global Registry of Acute Coronary Events (GRACE).

Methods

Full details of the GRACE rationale and methodology have been published.[12] In brief, GRACE is designed to reflect an unbiased population of patients with ACS in each geographic region. Currently, 94 hospitals organized into geographic clusters located in 14 countries are participating in this study. Clusters sites were selected to ensure that patient populations with varying demographic, clinical, and treatment characteristics were included. Hospital systems of different sizes, types, and treatment and diagnostic capabilities were included. The mean number of hospital beds was 426; mean number of coronary care unit (CCU) beds was 10; mean number of ACS admissions per year was 511; 96% of hospitals had a CCU; 87% had emergency departments; 65% of hospitals had access to a catheterization laboratory; and 48% were able to carry out open heart surgery.

Patients had to be at least 18 years old and alive at the time of hospital presentation, be admitted for ACS as a presumptive diagnosis, and have at least one of the following: electrocardiographic changes consistent with ACS, serial increases in serum biochemical markers of cardiac necrosis, and/or documentation of coronary artery disease. The qualifying ACS must not have been precipitated or accompanied by a significant comorbidity (eg, motor vehicle accident, trauma, severe gastrointestinal bleeding, operation or procedure). At approximately 6 months after hospital discharge, patients are followed up to ascertain the occurrence of selected long-term study outcomes. Where required, study investigators received approval from their local hospital ethics or institutional review board, and a signed consent form for follow-up contact was obtained.

Demographic characteristics, medical history, presenting symptoms, duration of prehospital delay, biochemical and electrocardiographic findings, treatment practices (use of interventions and procedures, medical treatments, lifestyle interventions), and hospital outcome data were collected through the use of a standardized case report form. Standardized definitions of all patient-related variables and clinical diagnoses were used.[12] All patients were assigned to one of the following categories: ST-segment elevation myocardial infarction (STEMI), non–ST-segment elevation myocardial infarction (NSTEMI), unstable angina, and other cardiac/noncardiac diagnoses.

The information on antithrombotic and antiplatelet treatment was collected in temporal categories: prehospital, within the first 24 hours, after the first 24 hours of hospitalization, and at discharge. Concomitant use of particular therapies was recorded.

Regional differences in the use of antithrombotic and antiplatelet therapies were analyzed according to four geographic regions: Australia, New Zealand and Canada (which were grouped together because they exhibited similar practice patterns with regard to the use of invasive procedures), Argentina and Brazil, Europe, and the United States.

Statistical analysis

Descriptive statistics (percentages for discrete variables, medians with 25^{th} and 75^{th} percentiles for continuous variables) were generated for baseline characteristics and frequencies of treatment used.

Comparisons between groups of patients were carried out through the use of χ^2 tests for differences in proportions of categorical variables and Kruskal-Wallis tests for differences in median values of continuous variables. All tests were 2-sided and considered significant at a value of $P < .05$.

In patients with NSTEMI or unstable angina, multivariable stepwise logistic regression analysis was performed to determine the best predictors of hospital use of "any heparin" (intravenous or subcutaneous UFH or LMWH), LMWH, thienopyridines, and GP IIb/IIIa inhibitors by using the following historic variables: age, sex, medical history of stroke, diabetes, myocardial infarction, hypertension, PCI or coronary artery bypass grafting (CABG); and clinical variables: length of hospital stay, admission heart rate, Killip class, cardiac arrest, ST-segment depression, hospital elevated cardiac enzyme concentrations, CABG, PCI, myocardial infarction after 24 hours, or reinfarction, or recurrent angina, congestive heart failure, or shock or pulmonary edema, creatinine clearance, hospital characteristics, and geographic region.

Final models identified independent predictors of the use of specific antithrombotic and antiplatelet agents, expressed in terms of odds ratio (OR) with 95% confidence intervals (CI). All final models were tested for overall goodness of fit by the Hosmer-Lemeshow test and for discriminative power by the *C* statistic. Statistical analyses were performed with the use of SAS software (version 8.2, SAS institute, Cary, NC).

Results

Demographic and clinical characteristics

Data from the first 12,665 patients with ACS, enrolled between April 1999 and March 2001, were analyzed (Table I). The baseline clinical characteristics of patients across ACS subgroups differed significantly. Patients with STEMI were significantly younger, and there was a higher proportion of men than in the groups with NSTEMI or unstable angina. When compared with patients in the NSTEMI and unstable angina groups, those with STEMI had a lower frequency of previous cardiac events, fewer risk factors, took longer to present to the hospital after the onset of symptoms, and stayed longer in hospital. The contribution of patients by geographic region is as follows: 21.7% USA, 42.9% Europe, 20.7% Argentina/Brazil, and 14.8% Australia/New Zealand/Canada.

Hospital antithrombotic treatment

The use of antithrombotic therapies differed for the three groups (Table II). UFH was used more frequently than LMWH. In STEMI patients, the use of UFH was higher than that for LMWH (66.8% vs 41.8%, respectively, $P < .0001$), whereas the difference was smaller for NSTEMI patients (59.4% vs 52.9%, respectively, *P*

Table I. Baseline clinical characteristics

	Total ACS, 12,665	STEMI, 4074 (32%)	NSTEMI, 3526 (28%)	Unstable angina, 5065 (40%)
Median age, y (range)	66.2 (56.1, 75.0)	64.3 (54.3, 73.9)	68.2 (57.6, 76.5)	66.4 (56.6, 74.6)
Male (%)	67.0	71.9	67.2	62.9
Medical history (%)				
Angina	66.6	48.6	65.7	81.9
Myocardial infarction	31.5	19.1	32.3	41.1
TIA/stroke	8.3	6.6	10.2	8.5
Diabetes mellitus	24.1	21.1	26.1	24.7
CHF	11.2	6.4	13.9	13.3
PCI	13.7	6.2	12.6	20.5
CABG	12.4	5.2	13.0	17.9
CAD	24.3	10.7	24.3	36.0
Hypertension	58.1	49.9	59.2	63.9
Hyperlipidemia	43.8	35.0	43.7	50.9
PAD	10.9	7.9	13.1	11.8
Atrial fibrillation	7.9	4.9	10.0	8.9
Median time from onset of symptoms to hospitalization, min (range)	2.5 (1.0, 4.0)	3.0 (2.0, 5.0)	2.0 (0.3, 4.0)	2.0 (0.0, 3.0)
Median length of hospital stay (CCU), days	6 (2.5)	8 (3.0)	6 (2.0)	5 (2.0)

CABG, Coronary artery bypass grafting; *CAD,* coronary artery disease; *CHF,* congestive heart failure; *PCI,* percutaneous coronary interventions; *TIA,* transient ischemic attack; *PAD,* peripheral artery disease.

Table II. Use of antithrombotic and antiplatelet treatments in hospital

	Total ACS, 12,665	STEMI, 4074 (32%)	NSTEMI, 3526 (28%)	Unstable angina, 5065 (40%)	*P**
Antithrombotic treatments					
UFH	7017 (56.6)†	2685 (66.8)†	2047 (59.4)†	2285 (46.3)	<.0001
LMWH	5797 (47.3)	1652 (41.8)	1803 (52.9)	2342 (47.9)	<.0001
Enoxaparin	4561 (37.4)‡	1230 (31.3)‡	1499 (44.1)‡	1832 (37.6)‡	<.0001
Other LMWH	1367 (11.2)	461 (11.7)	349 (10.3)	557 (11.4)	.1417
Oral anticoagulants	834 (6.8)	301 (7.5)	264 (7.7)	269 (5.5)	<.0001
No antithrombotic agent	1967 (15.8)	616 (15.3)	370 (10.6)	981 (19.0)	<.0001
Antiplatelet treatments					
Aspirin	11553 (92.3)	3840 (94.7)	3211 (92.0)	4502 (90.6)	<.0001
Ticlopidine/clopidogrel	3694 (30.0)	1533 (38.3)	1055 (30.7)	1106 (22.6)	<.0001
Ticlopidine/clopidogrel (no aspirin)	287 (2.2)	80 (2.0)	76 (2.1)	131 (2.6)	.0371
IV GP IIb/IIIa	2092 (16.7)	996 (24.5)	732 (20.9)	364 (7.3)	<.0001
No antiplatelet agent	612 (5.0)	118 (3.0)	179 (5.1)	315 (6.4)	<.0001

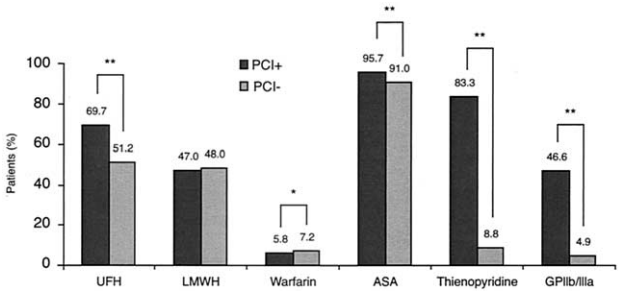
ACS, Acute coronary syndrome; *IV GP IIb/IIIa,* intravenous glycoprotein IIb/IIIa inhibitor; *LMWH,* low-molecular-weight heparin; *NSTEMI,* non-ST−segment elevation myocardial infarction; *STEMI,* ST-segment elevation myocardial infarction; *UFH,* unfractionated heparin.
*Global *P* values across the 4 categories.
†UFH versus LMWH $P < .0001$.
‡Enoxaparin versus other LMWH $P < .0001$.

$< .0001$). Patients with unstable angina were treated slightly more frequently with LMWH than with UFH. The most frequently used LMWH for treatment of patients with ACS was enoxaparin (37.4% vs 11.2% for other LMWHs, $P < .0001$). Less than 8% of patients were treated with oral anticoagulants. A total of 15.8% of patients did not receive either UFH or LMWH.

Hospital antiplatelet therapy

More than 90% of patients were treated with aspirin (Table II). The highest proportion who received aspirin were those with STEMI. Approximately one third of patients with ACS (22.6% to 38.3%) were treated with thienopyridines (ticlopidine or clopidogrel), and the highest rate of use was in patients

Figure 1



Use of antithrombotic and antiplatelet therapies in patients who did or did not undergo PCI. *ASA,* Aspirin; *GP IIb/IIIa,* glycoprotein IIb/IIIa inhibitor; *LMWH,* low-molecular-weight heparin; *UFH,* unfractionated heparin. *$P \leq .05$; **$P < .0001$

with STEMI (38.3%). Only 8.8% of patients received a thienopyridine without undergoing PCI. Of all patients with ACS who did not receive aspirin in the hospital (7.7%), only 30.8% were given thienopyridines. Clopidogrel was used 2 to 4 times more frequently than ticlopidine (STEMI, 644 vs 305, $P < .0001$; NSTEMI, 502 vs 131, $P < .0001$; unstable angina, 478 vs 254, $P = .0002$).

Intravenous GP IIb/IIIa inhibitors were used to treat 16.7% of patients with ACS. The highest use was in STEMI (24.5%). Five percent of patients with ACS received no aspirin, thienopyridines, or GP IIb/IIIa inhibitors.

Concomitant therapy with PCI

PCI had a major impact on the use of most antithrombotic and antiplatelet therapies (Figure 1, Tables III and IV). PCI was performed in 27.8% of all patients with ACS. Treatment with UFH, aspirin, thienopyridines, and platelet GP IIb/IIIa inhibitors was significantly more frequent in patients treated with PCI. This difference was particularly noticeable for GP IIb/IIIa inhibitors and thienopyridines. LMWH was used as frequently in patients who underwent PCI as in those who did not, whereas oral anticoagulants were given significantly less frequently to patients who had undergone PCI. Among patients who underwent PCI during their hospital stay, 46.6% received a GP IIb/IIIa inhibitor. Conversely, of those who received a GP IIb/IIIa inhibitor, 21.0% did not undergo PCI.

Therapies and troponin positivity

The use of antithrombotic and antiplatelet therapies in troponin-positive and troponin-negative NSTEMI or unstable angina patients is shown in Figure 2. Troponin levels were determined in 4511 NSTEMI or unstable angina patients and were found to be positive in 49.8% of these patients. UFH, LMWH, thienopyridines, and platelet GP IIb/IIIa inhibitors were used significantly more frequently in troponin-positive patients compared with troponin-negative patients. The use of oral anticoagulants and aspirin was not influenced by troponin status.

Use of therapies during hospitalization and at discharge

The timing of use of antithrombotic and antiplatelet agents in patients with ACS varied among therapies. An increase in the use of LMWHs, oral anticoagulants, and thienopyridines after the first 24 hours was revealed, whereas the use of UFH, aspirin, and GP IIb/IIIa inhibitors declined. During hospitalization, 25% of patients were given three, 13% four, and 4% five antithrombotic and/or antiplatelet agents.

At discharge, aspirin was used in 87.2% of patients and thienopyridines in 28.6%. Approximately 91% of patients received aspirin, ticlopidine, or clopidogrel or a combination of aspirin and a thienopyridine. Combined therapy of aspirin and ticlopidine or clopidogrel was used in 21.0% of all patients with ACS. In addition to this combination, therapy with oral anticoagulant at discharge was recorded in 0.8% of patients.

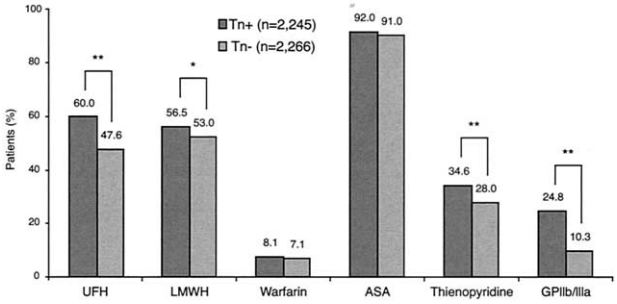
Therapies in various geographic regions

Aspirin was used with a similar high frequency across all regions (Figure 3). UFH was used most frequently in the US centers (76.1%) and least frequently in European centers (44.9%). This contrasts with LMWHs, which were most frequently used in European centers (64.9%) and least frequently used in the US centers (12.6%). Oral anticoagulants were used most frequently in the US centers (10.0%), whereas their use in other regions ranged from 4.7% to 8.8%. The use of thienopyridines was highest in the United States (39.2%) and lowest in Australia/New Zealand/Canada (18.7%). GP IIb/IIIa inhibitor use was also more frequent in the United States (32.7%) than other geographic regions (8.3% to 15.2%). For thienopyridines, these geographic differences appear to largely parallel the use of PCI.

Factors associated with the use of antithrombotic and antiplatelet agents

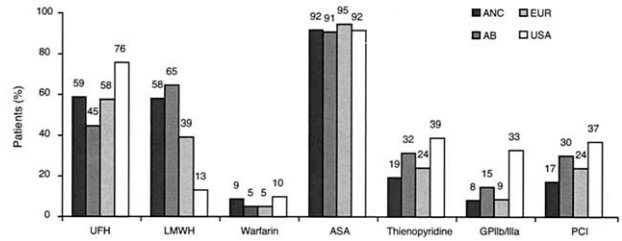
Multivariable logistic regression models were built to determine independent variables indicating the use of any heparin, LMWH, thienopyridines, and GP IIb/IIIa inhibitors in patients with NSTEMI or unstable angina (Table IV). Variables associated with the use of any heparin were any significant enzyme elevation, CABG, infarction 24 hours after admission or reinfarction or angina, or residence in Europe, Argentina/Brazil, or

Figure 2



Use of antithrombotic and antiplatelet therapies in troponin-positive and troponin-negative NSTEMI or unstable angina patients. *ASA,* Aspirin; *GP IIb/IIIa,* glycoprotein IIb/IIIa inhibitor; *LMWH,* low-molecular-weight heparin; *UFH,* unfractionated heparin; *Tn+,* troponin positive; *Tn−,* troponin negative; unfractionated heparin. *$P = .02$; **$P < .0001$

Figure 3



Use of antithrombotic and antiplatelet therapies and PCI by geographic region. *ANC,* Australia/New Zealand/Canada; *A/B,* Argentina/Brazil; *EUR,* Europe; *USA,* United States; *ASA,* aspirin; *GP IIb/IIIa,* glycoprotein IIb/IIIa inhibitor; *LMWH,* low-molecular-weight heparin; *UFH,* unfractionated heparin.

Table III. Therapies in patients who did or did not undergo percutaneous coronary intervention

	Total ACS (n = 12,665)		STEMI (n = 4074)		NSTEMI (n = 3526)		UA (n = 5065)	
	With PCI, 3523 (100%)	Without PCI, 8911 (100%)	With PCI, 1635 (100%)	Without PCI, 2416 (100%)	With PCI, 988 (100%)	Without PCI, 2509 (100%)	With PCI, 900 (100%)	Without PCI, 3986 (100%)
UFH 6910 [100]	2414 (69.7) [34.9]	4496 (51.2)† [65.1]	1212 (74.1) [45.5]	1454 (60.2)† [54.5]	680 (68.8) [33.6]	1346 (53.4)† [66.4]	522 (58.0) [23.5]	1696 (42.5)† [76.5]
LMWH 5745 [100]	1609 (47.0) [28.0]	4136 (47.5) [72.0]	658 (40.2) [39.9]	990 (41.0) [61.1]	520 (52.6) [29.0]	1276 (50.8) [71.0]	431 (47.9) [18.7]	1870 (46.9) [81.3]
Oral anticoagulants 826 [100]	199 (5.8) [24.1]	627 (7.2)* [75.9]	125 (7.6) [41.7]	175 (7.2) [58.3]	42 (4.2) [16.0]	221 (8.8)† [84.0]	32 (3.5) [12.2]	231 (5.8)* [87.8]
Aspirin 11,405 [100]	3351 (95.7) [29.4]	8054 (91.0)† [70.6]	1563 (95.6) [40.6]	2254 (93.3)* [59.1]	939 (95.0) [24.5]	2245 (89.5)† [70.5]	849 (94.3) [19.3]	3555 (89.2)† [80.7]
Ticlopidine/Clopidogrel 3663 [100]	2894 (83.3) [79.0]	769 (8.8)† [21.0]	1353 (82.7) [88.4]	178 (7.4)† [11.6]	824 (83.4) [78.2]	230 (9.1)† [21.8]	717 (79.7) [66.5]	361 (9.1)† [33.5]
IV GP IIb/IIIa 2068 [100]	1633 (46.6) [79.0]	435 (4.9)† [21.0]	856 (52.3) [86.2]	137 (5.7)† [13.8]	518 (52.5) [71.6]	206 (8.2)† [28.5]	259 (28.8) [73.8]	92 (2.3)† [26.2]

(%), Percentage of patients treated with listed medications among patients with and without PCI; [%], percentage of patients with or without PCI among patients treated with listed medications.
P value with PCI versus without PCI:
*$P < .01$.
†$P < .0001$.

Australia/New Zealand/Canada (relative to the United States). Independent predictors associated with the use of LMWH were length of hospital stay and residence outside the United States. In-hospital PCI was the most important variable associated with the use of thienopyridines or GP IIb/IIIa inhibitors.

Discussion

In this ongoing multinational registry of patients hospitalized with ACS, the antithrombotic agents UFH and LMWH were used more frequently for patients with ACS than in the PRAIS-UK[13] and ENACT[14] studies, which were conducted earlier than the GRACE registry. UFH was used more frequently than LMWH in the current study, particularly in those undergoing coronary interventions. This level of use is in agreement with the guidelines, which recommend both agents equally. However, this pattern of use may change as data emerge regarding the use of LMWH with fibrinolytics[18] in patients undergoing PCI and with GP IIb/IIIa blockers.[16,17]

Table IV. Factors coinciding with hospital use of any heparin, low-molecular-weight heparin, ticlopidine or clopidogrel, and glycoprotein IIb/IIIa inhibitors

Factor	Any heparin	LMWH	Thienopyridines	GP IIb/IIIa inhibitor
Stroke	0.7 (0.56–0.90)			
Length of hospital stay		1.3 (1.13–1.41)		
ST-segment depression	1.3 (1.05–1.48)	1.3 (1.15–1.43)		
Any significant enzyme elevation	2.0 (1.67–2.40)			2.7 (2.29–3.25)
Creatinine clearance <30 mL/min	0.7 (0.52–0.87)			0.5 (0.37–0.78)
Heart rate >100 beats/min			0.7 (0.59–0.94)	
Inhospital PCI	1.5 (1.25–1.89)	1.3 (1.16–1.50)	2.7 (2.29–3.25)	13.1 (11.00–15.67)
Inhospital CABG	2.3 (1.55–3.42)			
Myocardial infarction >24 or reinfarction or recurrent angina	2.1 (1.57–2.76)	1.3 (1.10–1.46)	1.3 (1.10–1.63)	
Hospital with access to a catheterization laboratory	1.7 (1.43–2.07)	1.3 (1.14–1.46)		
Geographic region*				
Europe	2.3 (1.89–2.75)	16.0 (13.68–19.00)	0.8 (0.71–1.00)	0.3 (0.22–0.33)
South America	2.8 (2.27–3.56)	4.5 (3.80–5.33)	0.6 (0.46–0.70)	0.2 (0.18–0.31)
Australia/New Zealand/Canada	5.0 (3.54–6.91)	13.5 (11.26–16.20)	0.5 (0.40–0.63)	0.2 (0.12–0.24)

Results from multivariable logistic regression analysis. Values expressed as adjusted odds ratios and 95% CIs. Hosmer and Lemeshow Goodness-of-Fit-Test: any heparin *P* value = .470, LMWH *P* value = .833, ticlopidine or clopidogrel *P* value = .615, GP IIb/IIIa inhibitors *P* value = .017. C-Statistics for any heparin = 0.70, LMWH = 0.76, ticlopidine or clopidogrel = 0.86, GP IIb/IIIa inhibitors = 0.86. Compared with USA.

Current data have been acknowledged in the new ACC/AHA guidelines for non–ST-elevation ACS. Anticoagulation with LMWH or UFH is recommended; however, it is stated that enoxaparin is preferable to UFH unless CABG is planned within 24 hours.[2] Oral anticoagulants were administered infrequently in the GRACE population, which is consistent with recommendations in the guidelines. The role of these agents is still uncertain in view of conflicting data from several studies.[18–22]

Data from the GRACE registry reveal a high frequency of aspirin administration. Surprisingly, however, 13% of patients with ACS did not receive aspirin at discharge, which is a strikingly higher rate than that reported for aspirin intolerance.[23] In contrast, thienopyridines were used relatively infrequently, and when administered they were given with aspirin in more than 92% of patients, usually in the context of PCI. Thienopyridines are recommended for the treatment of patients who are unable to take aspirin or for use in combination with aspirin for the short-term treatment of patients receiving a stent.[2] The CURE trial, which was published subsequent to the period of data collection for this study, demonstrated the efficacy of clopidogrel in addition to aspirin[9] in patients with ACS.

The use of intravenous GP IIb/IIIa inhibitors was relatively infrequent in patients participating in GRACE. In patients with NSTEMI and unstable angina, approximately one quarter of those who received a GP IIb/IIIa inhibitor were treated noninvasively. The GUSTO IV ACS trial[24] does not support the use of abciximab in medically treated patients with non–ST-elevation with ACS. By contrast, in the PURSUIT study, eptifibatide reduced the risk of death or nonfatal myocardial infarction in patients with non–ST-elevation with ACS when compared with placebo.[25] The use of PCI in patients with ACS was a major factor influencing the use of GP IIb/IIIa inhibitors and thienopyridines. This was demonstrated in the multivariable logistic regression model and is a strategy supported by results from clinical trials.[10,26,27]

The use of UFH, LMWH, thienopyridines, and GP IIb/IIIa inhibitors was significantly greater in troponin-positive patients, who are at higher risk than troponin-negative patients. This practice is in agreement with current guidelines.[2] Nevertheless, relatively high numbers of troponin-negative patients were treated with agents whose efficacy has been questioned in this group. Those patients could, however, have significant electrocardiographic changes or other features that would warrant therapy.

Striking differences in clinical practice patterns based on the geographic distribution of patients were shown. Only aspirin was used with similar high frequencies across all regions. These variations are likely to reflect differences in drug registration, cost, and frequency of tertiary centers. Another factor that determines the use of these therapies is the use of an invasive or conservative strategy. The frequency of invasive treatment of patients with ACS correlates closely with the availability of appropriate facilities.[6,28,29] Variations are more related to geographic differences in the availability of catheterization facilities or PCI than to patient type or site. Interestingly, this study reveals

that more than 40% of patients with ACS were treated with three or more antithrombotic and antiplatelet agents. This raises important issues regarding the cost and safety of current patterns of use of these treatments.

Limitations of the analysis

Particular steps were taken in the design of this registry to minimize bias and reflect geographic practice patterns. Nevertheless, the project is subject to limitations that may reduce the generalizability of the findings. Participating clusters may reflect regional practices and outcomes, but not necessarily those of the country. Important geographic regions are not represented. However, GRACE is a large multinational ACS registry, and its size may help to compensate for random fluctuations in patient characteristics.

Conclusions

The GRACE study shows important geographic and practice variations in the use of antithrombotic and antiplatelet agents in comparison with evidence from large-scale randomized trials and practice guidelines. Well-established medications such as aspirin, LMWH, and intravenous GP IIb/IIIa inhibitors are used at suboptimal frequencies. The GRACE study will allow the detection of changes in the patterns of use of these medications over time.

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